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| EXAMINER |
|---|
| BERTAGNA, ANGELA MARIE |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/517,544 | HAYASHIZAKI ET AL. | |
| | Examiner | Art Unit | |
| | Angela M. Bertagna | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *23 July 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *9,10,12-17,19-25,34-51,57 and 58* is/are pending in the application.

4a) Of the above claim(s) *34-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,12-17,19-25,57 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of the Application*

1. Applicant's response filed on July 23, 2010 is acknowledged. Claims 9, 10, 12-17, 19-25, 34-51, 57, and 58 are currently pending. In the response, Applicant amended claims 16, 17, 24, 25, and 58. Claims 34-51 remain withdrawn from consideration as being drawn to a non-elected invention.

The following include new grounds of rejection necessitated in part by Applicant's amendments to the claims. Any previously made objections or rejections not reiterated below have been withdrawn. Applicant's arguments filed on July 23, 2010 have been fully considered and were persuasive in part. Since not all of the new grounds of rejection were necessitated by Applicant's amendment, this Office Action is made **NON-FINAL**.

### *Claim Rejections - 35 USC § 102*

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Claims 17, 19-21, and 23-25 are rejected under 35 U.S.C. 102(e) as being anticipated by Pedersen (US 2003/0113737 A1; cited previously).

These claims are drawn to a method for preparing a double-stranded DNA fragment corresponding to the 5' end of an mRNA comprising linker ligation and restriction enzyme digestion.

Regarding claim 17, Pedersen teaches a method for preparing a double-stranded DNA fragment comprising a nucleotide sequence corresponding to the most 5' end of an mRNA that comprises:

(a) preparing a nucleic acid that corresponds to a nucleotide sequence of the 5' end of an mRNA (see Figure 12, steps I & II and paragraphs 61, 254 and 261-262, where the decapped mRNA is prepared)

(b) attaching at least one linker to the nucleic acid by:

(i) attaching a linker to an end region corresponding to the most 5' end of the mRNA, wherein the linker contains a recognition sequence for a restriction enzyme that cleaves at a site different from its recognition sequence (see Figure 12, step III and paragraphs 61, 254 and 261-262, where the adapter, which has recognition sequences (A) and (B) for a nicking endonuclease and a Type IIS restriction enzyme, respectively, is ligated to the 5' end of the decapped mRNA)

(ii) synthesizing a first strand cDNA using the mRNA having the linker attached as a template (see Figure 12, step IV and paragraphs 61, 254 and 261-262, where reverse transcription using random decamers is taught)

(iii) removing the mRNA (see Figure 12, step V and paragraphs 61, 254 and 261-262, where the second strand synthesis step inherently removes the mRNA by strand displacement)

(iv) synthesizing a second strand cDNA using the first strand cDNA as a template (see Figure 12, step V and paragraphs 61, 254 and 261-262)

(c) cleaving the nucleic acid with the Type IIS restriction enzyme and the nicking enzyme (paragraph 263)

(d) collecting the resulting fragment corresponding to the most 5' end of the mRNA (see Figure 14 and paragraph 63, and paragraphs 262-264; see also Figure 12 and paragraph 61, which teach that the cleavage with the nicking enzyme and the Type IIS restriction enzyme as described in paragraph 263 generates a fragment corresponding to the 5' terminus of the mRNA).

Regarding claim 19, Pedersen teaches that the second strand cDNA is synthesized using a primer that has the sequence of the linker (paragraphs 61 and 261). These primers are inherently partially complementary to the linker region (*i.e.*, they contain at least 2 consecutive nucleotides that are complementary to the linker region - see pages 30-33 for specific examples of such adapters).

Regarding claims 20 and 21, Pedersen teaches that a selective binding substance, specifically biotin, is attached to the oligonucleotide primers used to synthesize second strand cDNA and that the products of the second strand synthesis reaction are recovered using a solid support having streptavidin immobilized thereupon (see paragraphs 262-264).

Regarding claims 23-25, Pedersen teaches that the restriction enzyme is a Class IIS restriction enzyme (see paragraphs 61, 254, and 262-263), such as Bpm I (paragraphs 785 & 791) or BsgI (page 31).

***Claim Rejections - 35 USC § 103***

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pedersen (US 2003/0113737 A1; cited previously) in view of Cocuzza et al. (US 5,484,701; cited previously).

Pedersen teaches the method of claims 17, 19-21, and 23-25, as discussed above.

Pedersen teaches that the oligonucoleotide primer used in the second strand cDNA synthesis step contains biotin to permit streptavidin-mediated capture rather than digoxigenin to permit capture with an anti-digoxigenin antibody (see above).

Cocuzza teaches a method for isolating primer extension products prior to electrophoresis comprising biotinylation of the primer extension product and isolation with a support-immobilized avidin (abstract and column 3, line 55 – column 4, line 20). Regarding claim 22,

Cocuzza teaches that biotinylated primer extension products may also be isolated using an antibody-antigen capture system, wherein the antigen digoxigenin is attached to the primer and the primer extension products are captured with a support-immobilized anti-digoxigenin antibody (column 7, lines 28-43). In this passage, Cocuzza further teaches that this system performs as well as the biotin-avidin system, and that methods for immobilizing antibodies on solid supports are known.

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to substitute the biotin-streptavidin capture method taught by Pedersen with the digoxigenin-anti-digoxigenin antibody capture method taught by Cocuzza. An ordinary artisan would have been motivated to do so with a reasonable expectation of success, since Cocuzza taught that digoxigenin-mediated capture was an art-recognized equivalent of the biotin-avidin capture method taught by Pedersen (column 7, lines 28-43). As noted in MPEP 2144.06, substitution of art-recognized equivalents known to be useful for the same purpose is *prima facie* obvious in the absence of unexpected results. In this case, no evidence of unexpected results with respect to the use of digoxigenin has been presented. Accordingly, the method of claim 22 is *prima facie* obvious over Pedersen in view of Coccuza.

6. Claims 9, 10, 12, 14-16, and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (WO 2002/088395 A1; newly cited) in view of Merenkova et al. (US 6,022,715 B1; cited previously).

These claims are drawn to a method for preparing a DNA fragment corresponding to the 5' end of an mRNA that comprises affinity purification based on the cap structure at the 5' end of mRNA, linker ligation, and digestion with a Type IIS restriction enzyme.

Zhang teaches a method for preparing a DNA fragment corresponding to the most 5' end of an mRNA (see abstract, Figure 1, and page 9).

Regarding claims 9, 10, 12, 14-16, and 58, Zhang teaches preparing a nucleic acid corresponding to the most 5' end of an mRNA via a method comprising (see Figure 1, pages 38-39, and Example 1 at pages 41-42): (i) synthesizing a full-length first-stranded cDNA molecule using mRNA as a template to produce cDNA/mRNA hybrids, (ii) attaching a linker to the 3' end of the resulting cDNA molecule, which corresponds to the 5'-most end of the mRNA, (iii) cleaving the nucleic acid with a restriction enzyme having its recognition site within the linker and its cleavage site within the cDNA molecule, and (iv) collecting a resulting DNA fragment that corresponds to the 5' most end of the mRNA.

Zhang suggests using the 5' cap structure and selective binding substances, such as biotin or digoxigenin, to isolate a 5' nucleic acid sequence tag (page 11, lines 8-16), but the disclosed methods do not comprise a step of selecting cDNA/mRNA hybrids that have the 5' cap structure of the mRNA using a selective binding substance that specifically recognizes the 5' cap structure as required by claims 9, 10, and 16 or a step of conjugating a selective binding substance to the 5' cap structure for subsequent purification of cDNA/mRNA hybrids in which the 5' cap structure is present as required by claims 12, 14, 15, and 58.

Merenkova teaches a method for isolating full-length cDNA molecules. The method of Merenkova comprises modifying the 5' cap structure of an mRNA to contain a molecule, such as

biotin or digoxigenin, that may be selectively captured by its binding partner (*i.e.,* streptavidin or an anti-digoxigenin antibody, respectively) immobilized on a solid support, such as magnetic beads, synthesizing first-strand cDNA using the modified mRNA molecules as a template to produce cDNA/mRNA hybrids, selectively capturing hybrids based on the modification present on the 5' cap, and digesting the mRNA component of the captured hybrids, thereby obtaining a full-length cDNA corresponding to the complete mRNA (see abstract, column 5, line 55 – column 6, line 38, column 6, line 60 – column 7, line 12).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to incorporate the biotin or digoxigenin-mediated capture step taught by Merenkova into the method described by Zhang. Since the method of Zhang was specifically designed to obtain nucleic acid sequence tags corresponding to the 5' most region of mRNA molecules, the ordinary artisan would have been motivated to ensure that only first-strand cDNA molecules produced from full-length mRNA molecules were used in the subsequent linker attachment and restriction enzyme digestion steps, thereby reducing the possibility of generating sequence tags from cDNA molecules produced from truncated mRNA molecules. Since Merenkova taught a method for isolating full-length mRNA molecules based on the presence of the 5' cap structure, which is only present in mRNAs that are not truncated at the 5' end, the ordinary artisan would have been motivated to incorporate the cap labeling and purification steps disclosed by Merenkova into the method of Zhang with a reasonable expectation of success. Thus, the methods of claims 9, 10, 12, 14-16, and 58 are *prima facie* obvious in view of the combined teachings of the cited references.

7. Claims 13 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al. (WO 2002/088395 A1; newly cited) in view of Merenkova et al. (US 6,022,715 B1; cited previously) and further in view of Edery et al. (Molecular and Cellular Biology (1995) 15(6): 3363-3371; cited previously) and further in view of Das et al. (Physiological Genomics (2001) 6: 57-80; cited previously).

The combined teachings of Zhang and Merenkova render obvious the methods of claims 9, 10, 12, 14-16, and 58 as discussed above.

These references do not teach using a cap-binding protein or a cap-binding antibody attached to a solid support to selectively capture mRNA/cDNA hybrids in which the mRNA component of the hybrid possesses the 5' cap structure as required by claims 13 and 57.

Edery teaches a method ("CAPture") for isolating full-length cDNA transcripts or cDNA transcripts having the most 5' end that comprises affinity capture using the cap-binding protein eIF-4e (see abstract). The method of Edery comprises the following steps: reverse transcribing mRNA to generate cDNA/mRNA hybrids, treating the reverse transcription reaction with RNase A treatment to remove contaminating single-stranded RNA, binding eIF-4e to the 5' cap structure of the mRNA component of the hybrids to selectively bind full-length mRNA/cDNA hybrids, and capturing the bound eIF-4e/mRNA/cDNA complexes using an anti-eIF-4e antibody conjugated to sepharose beads (see page 3364, column 2 – page 3365, column 1 and Figure 4).

Das reviewed methods for obtaining full-length cDNA molecules. Das compared the affinity selection methods based on biotin (*i.e.,* the cap trapper method) and Edery (*i.e.,* affinity selection using the cap-binding protein eIF-4e) and reported that the cap trapper method was not specific. Specifically, Das stated:

> [I]f we compare the ability of cap trapper to discriminate between cDNA duplex with capped mRNA (generated *in vitro*) or duplexed with uncapped mRNA (generated *in vitro*), then we are unable to obtain specific selection of capped over uncapped transcripts (J. Pelletier, data not shown). This is likely due to the fact that biotin-hydrazide can also react with unoxidized RNA due to incipient reaction of cytosine residues. Hence, addition of biotin is not solely directed toward the cap structure. Also, it is important to note that the oxidation reaction with $NaIO_4$ is difficult to control, and the molar ratio of periodate to substrate is important, otherwise one gets destruction of base rings (page 73).

It would have been *prima facie* obvious for one of ordinary skill in the art at the time of invention to substitute the affinity selection method of Edery based on eIF-4e for the biotin-based capture method taught by Merenkova when practicing the method resulting from the combined teachings of Zhang and Merenkova. An ordinary artisan would have been motivated to do so with a reasonable expectation of success, since Das taught that the affinity selection method based on eIF-4e-mediated capture was more specific than the biotin-based cap trapper method and advantageously avoided the use of the potentially RNA-degrading reagent $NaIO_4$ (see above). Thus, the methods of claims 13 and 57 are *prima facie* obvious in view of the combined teachings of the cited references.

### ***Response to Arguments***

8. Applicant's arguments filed on July 23, 2010 have been fully considered, and they were persuasive in part.

**Objection to the Specification**

Applicant argues that the claim amendments, which delete elements not finding proper antecedent basis in the specification, have obviated the previously made objection (page 9). This argument was persuasive, and, accordingly, the objection has been withdrawn.

**Objection to claim 17**

Applicant argues that the claim amendments have obviated the previously made objection (page 10). This argument was persuasive, and, accordingly, the objection has been withdrawn.

**Rejection of claim 24 under 35 U.S.C. 112, second paragraph**

Applicant argues that the claim amendments have obviated the previously made rejection (page 10). This argument was persuasive, and, accordingly, the rejection has been withdrawn.

**Rejection of claims 17, 19-21, & 23-25 under 35 U.S.C. 102(e) as being anticipated by Pedersen**

Applicant first argues that the amendment to step (d) of claim 17 has obviated the previously made rejection (page 11). This argument was not persuasive, because the teachings of Pedersen still anticipate the methods of claims 17, 19-21, and 23-25. As discussed above, Pedersen teaches in Figure 12 and paragraphs 256-263 a method that comprises obtaining an mRNA molecule, ligating a linker to the 5' end of the mRNA molecule, performing first strand cDNA synthesis, removing the mRNA molecule, performing second strand cDNA synthesis using the first strand cDNA molecule as a template, cleaving the resulting double-stranded cDNA molecule with a Type IIS restriction enzyme, which has its recognition site within the linker and its cleavage site within the double-stranded cDNA molecule, and, immediately following this step, collecting a resulting double-stranded cDNA molecule corresponding to the 5' most end of the mRNA molecule (see, in particular, paragraph 263, where Pedersen teaches collecting the double-stranded proximal cDNA fragment, which corresponds to the 5' most end of the mRNA molecule (see Figure 12) after the Type IIS digestion step and before the step of nicking enzyme digestion). Although Applicant correctly notes at page 10 of the response that

the method disclosed by Pedersen comprises the additional steps of digestion with a nicking enzyme to release a single-stranded cDNA fragment that is subsequently analyzed by ligation to another oligonucleotide linker, the additional steps occur after the steps of the method corresponding to steps (a)-(d) of the instant claim 17, and, therefore, do not change the fact that the method of Pedersen comprises the claimed method. It is noted that the claimed methods are written in open, "comprising" language, and, therefore, they do not exclude the presence of additional steps conducted after step (d) of the instant claim 17.

Applicant also argues that the fragment collected by Pedersen does not correspond to the 5' most end of the mRNA molecule as required by independent claim 17 (page 11). This argument was not persuasive, because the proximal double-stranded cDNA fragment collected after Type IIS digestion and before nicking enzyme digestion as described by Pedersen at paragraph 263 comprises a region corresponding to the most 5' end of the mRNA molecule as required by claim 17.

Since Applicant's arguments were not persuasive, the rejection has been maintained with modifications to address the claim amendments.

**Rejection of claim 22 under 35 U.S.C. 103(a) as being unpatentable over Pedersen and Cocuzza**

Applicant argues that the teachings of Cocuzza do not remedy the deficiencies in Pedersen with respect to independent claim 17 (page 12). This argument was not persuasive, because, as discussed above, Pedersen teaches all of the elements of claims 17, 19-21, and 23-25. Cocuzza is only relied upon for those teachings that are relevant to claim 22. Since Applicant's arguments were not persuasive, the rejection has been maintained.

**Rejection of claims 9, 10, 12, 14, 16, and 58 under 35 U.S.C. 103(a) as being unpatentable in view of the combined teachings of Shibata, Carninci, and Kaufman**

Applicant argues that the combined teachings of the cited references do not suggest preparing a double-stranded fragment corresponding to the 5' most end of an mRNA molecule as required by the rejected claims (page 13). More specifically, Applicant argues that the primary reference, Shibata, teaches preparation of full-length cDNA libraries rather than the preparation of double-stranded fragments corresponding to the 5' most end of an mRNA molecule as required by the claims, and that the secondary reference (Kaufman) does not remedy this deficiency in the primary reference (page 13). This argument was persuasive, and, accordingly, the rejection has been withdrawn, since the combined teachings of the cited references do not suggest the production of sequence tags corresponding to the most 5' portion of an mRNA molecule. The previously made rejections of claims 13, 15, and 57 under 35 U.S.C. 103(a) based on the primary combination of Shibata, Carninci, and Kaufman have also been withdrawn in view of Applicant's arguments with respect to the primary combination of references.

***Conclusion***

9. No claims are currently allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANGELA BERTAGNA whose telephone number is (571)272-8291. The examiner can normally be reached on M-F, 9- 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached at 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Angela M Bertagna/
Examiner, Art Unit 1637